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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LI, QIAN J	

ART UNIT	PAPER NUMBER
1632	22

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/517,898	Applicant(s) VOGELS ET AL.	
	Examiner Q. Janice Li	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,18-22,27 and 35-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,18-22,27 and 35-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *3/3/00, 10/24/02* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I in Paper No. 13 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 12-17, 23-26, and 28-34 have been canceled. Claims 35-40 and 51-56 are newly added. Claims 51-56 have been renumbered as claims 41-46 according to 37 C.F.R. 1.126 (see MPEP 608.01 (j) and 608.01 (n)/**IV**). Election was made **without** traverse in Paper No. 13.

Claims 1-11, 18-22, 27, and 35-46 are under current examination.

Drawings

This application contains color photographs. Color photographs and color drawings are acceptable only for examination purposes unless a petition filed under 37 CFR 1.84(a)(2) is granted permitting their use as acceptable drawings. In the event that applicant wishes to use the drawings currently on file as acceptable drawings, a petition must be filed for acceptance of the color photographs or color drawings as acceptable drawings. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three sets of color drawings or color photographs, as appropriate, and an amendment to the first paragraph of the brief description of the drawings section of the specification which states:

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the U.S. Patent and Trademark Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings have been satisfied.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11, 18-22, 27, and 35-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

These claims are vague and indefinite because of the claim recitation "fibroblast-like or macrophage-like cells". The specification fails to define the term besides giving an example of "synoviocyte", which is not a recognized term in standard English Dictionary or Stedman's Medical Dictionary, thus, it is unclear what type of cells the claims embrace, the metes and bounds of the claims are unclear. For purpose of compact prosecution, the term "fibroblast-like or macrophage-like cells" would be interpreted as including macrophages, dendritic cells, epithelial or endothelial cells, and fibroblast cells (which contained in synovial cavity).

Claim 2 recites, "partially reduced tissue tropism", it is unclear which term and characteristic "partially" describes, "reduced" or "tropism", the baseline relative to the reduction, and/or what degree of reduction is considered "partially", thus, the metes and

bounds of the claim are unclear. Likewise, claim 3 recites the tissue tropism being deprived in part, while "deprive" means taking something away, it is unclear, how it could be taking away in part, and it is unclear which part of the tropism has been deprived, thus, the metes and bounds of the claims are unclear.

Claim 27 provides a method for delivering nucleic acid to fibroblast-like or macrophage-like cells, which embraces both in vitro and in vivo methods. But the claim does not set forth any steps involved in the in vivo method/process, other than "introducing the vehicle of claim 1", it is unclear how the vehicle is introduced to the particular cells. Method claims need not recite all operating details but should at least recite positive, active steps so that the claims will set out and circumscribe a particular area with a reasonable degree of precision and particularity and make clear what subject matter that claims encompass as well as make clear the subject matter from which others would be precluded, *Ex parte Erlich*, 3 USPQ2d 1011 at 6.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11, 18-22, 27, and 35-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement;* Federal Register/ Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

Claim 1 recites "fibroblast-like or macrophage-like cells", although macrophage and fibroblast cells are well-known in the art, the characteristics of fibroblast-like or macrophage-like cells are not as well-defined, and the specification does not define the term, the only description regarding the term is limited to synovial cells, which by itself, embrace endothelial, epithelial, fibroblast, and perhaps lymphocytes as indicated in the teachings of *Shang et al* (J Immunol 1998;160:467-74) and *Lazarovits et al* (J Immunol 1993;151:6482-9). Therefore, the specification fails to provide adequate description for the broadly claim language in terms of distinguishing identifying characteristics, and fails to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 2 and 3 recite a nucleic acid delivery vehicle having reduced tissue tropism for liver cells, given the broadest reasonable interpretation, the claims embrace

a genus of molecules that have reduced liver tropism, where there are uncountable means of achieving such effect, the only means of reduction disclosed in the specification is incorporate the Ad16 fiber with that of Ad5, the specification fails to teach the chemical or physical structures of a common attribution or a consensus feature by which the liver tropism would be reduced, therefore, fails to provide an adequate description for the genus of said vehicles. The Revised Interim Guidelines state "THE CLAIMED INVENTION AS A WHOLE MAY NOT BE ADEQUATELY DESCRIBED IF THE CLAIMS REQUIRE AN ESSENTIAL OR CRITICAL ELEMENT WHICH IS NOT ADEQUATELY DESCRIBED IN THE SPECIFICATION AND WHICH IS NOT CONVENTIONAL IN THE ART" (Column 3, page 71434), "WHEN THERE IS SUBSTANTIAL VARIATION WITHIN THE GENUS, ONE MUST DESCRIBE A SUFFICIENT VARIETY OF SPECIES TO REFLECT THE VARIATION WITHIN THE GENUS", "IN AN UNPREDICTABLE ART, ADEQUATE WRITTEN DESCRIPTION OF A GENUS WHICH EMBRACES WIDELY VARIANT SPECIES CANNOT BE ACHIEVED BY DISCLOSING ONLY ONE SPECIES WITHIN THE GENUS" (Column 2, page 71436). Considering numerous viruses present in the universe, and embraced by the claims, the peptide heterogeneity of the capsid proteins, and the complex three-dimensional structure of the combination of these proteins, the one disclosed chimeric fibers of Ad5/Ad16 is not the representative species of the genus.

An adequate written description for an active agent requires more than a mere statement that it is part of the invention; what is required is a description of the chemical structures and physical properties itself. It is not sufficient to define the vehicles solely by its principal biological property, i.e. "a tissue tropism for fibroblast-like cells", or "reduced liver tropism", or providing a desired tissue tropism, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any

vehicle with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all vehicles that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). With respect to the method claims, adequate description of the methods first requires an adequate description of the materials, i.e. specific chemical and physical properties of a chemical, or the structure of the vehicle, which provide the means for practicing the invention. The court has made it very clear "CONCEPTION OF CHEMICAL COMPOUND REQUIRES THAT INVENTOR BE ABLE TO DEFINE COMPOUND SO AS TO DISTINGUISH IT FROM OTHER MATERIALS, AND TO DESCRIBE HOW TO OBTAIN IT, RATHER THAN SIMPLY DEFINING IT SOLELY BY ITS PRINCIPAL BIOLOGICAL ACTIVITY". *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

Claims 4 and 5 are drawn to providing the desired tissue tropism by at least a part of a virus capsid or a functional derivative and/or analogue thereof, and preferably from two different viruses, the specification fails to teach what are these viruses, which particular capsid protein region of a given virus would have such functional features, and which combination of two such regions would achieve the reduced liver tropism and having a tissue tropism for fibroblast-like or macrophage-like cells, which part of a given protein is considered as functional derivative and/or analogues, which combination of the functional derivative and analogue would achieve the reduced liver tropism and

having a tissue tropism for fibroblast-like or macrophage-like cells, the brief general reviews regarding what is known in the art in altering tissue tropism could not supplement the specific description needed as to the generic claims of a nucleic acid delivering vehicle having reduced liver tropism and a tissue tropism for fibroblast-like or macrophage-like cells, thus, fails to provide adequate description for the broad claims.

With regards to the functional derivative and/or analogue of the capsid proteins of a virus, the limitation is obvious generic to a considerable number of polypeptides varying in the length of the peptides, the homologies among the sequences, and the function of the polypeptides. The specification fails to provide an adequate description to teach the structure-function relationship of these polypeptides with regard to their function as biologically active components for providing a particular tissue tropism, and accordingly does not provide a reasonable guide for those seeking to practice the invention. The proper function of a capsid protein in cell binding and internalization is determined by the three dimensional structure of the proteins. It is unpredictable without undue experimentation to determine which fragment of the certain capsid protein would form a functional conformation for the specific cell receptor binding. The specification has not set forth in terms of structural or distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed genus of the invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the

'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the genus of *capsid proteins from any type of viruses* that have a tissue tropism for fibroblast-like or macrophage-like cells, and a reduced tropism for liver cells, and it fails to provide adequate written description for a genus of means in altering tissue tropism of any nucleic acid delivery vehicle. Therefore, only the described chimeric Ad5.Fib16 adenoviral vector meets the written description provision of 35 U.S.C. §112, first paragraph.

Claims 1-11, 18-22, 27, and 35-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention (see *In re Wands*, 858 F. 2d 731, 737, 8 USPQ 2d 1400, 1404, 1988). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided.

The claims embrace any nucleic acid delivery vehicle having a tissue tropism for fibroblast-like or macrophage-like cells, and a reduced tropism for liver cells, and methods of using such, however, as indicated *supra* in the written description section, the specification fails to provide an adequate description for the broad classes of vehicles encompassed by the claims, and fails to disclose whether the Ad5.Fib16 vector could selectively target all fibroblast-like or macrophage-like cells. Since the disclosure fails to describe the common attributes or characteristics that identify members of the claimed genus, Ad5.Fib16.LacZ and synovial fibroblast alone is insufficient to describe the genus. This is because that protein chemistry is probably one of the most unpredictable areas of biotechnology. Although the polynucleotide-coding region determines amino acid sequence of the protein, it is the conformation of the three-dimensional structures that allows the protein to function and carry out the messages of the genome. *Bowie et al* (Science 1990 Mar; 247:1306-10) teach certain position in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or none at all (page 1306, column 2). *Wickham et al* (US 6,455,314) teach particularly regarding altering cell affinity of

adenovirus, "FAR MORE DESIRABLE IS AN ADENOVIRUS WHICH INFECTS ONLY A DESIRED CELL TYPE, AN APPROACH REFERRED TO AS "ALTERNATIVE TARGETING", "EFFORTS AIMED AT ABROGATING NATIVE ADENOVIRAL CELL AFFINITY HAVE FOCUSED LOGICALLY ON CHANGING THE FIBER KNOB. THESE EFFORTS HAVE PROVEN DISAPPOINTING, LARGELY BECAUSE-THEY FAIL TO PRESERVE THE IMPORTANT FIBER PROTEIN FUNCTIONS OF STABLE TRIMERIZATION AND PENTON BASE BINDING" (column 3, lines 21-55). Neither art of record nor the instant specification teaches a core structure-functional relations that target the vector only to certain type of cells. One cannot extrapolate the teachings of the specification to the scope of the claims because the skilled artisan cannot envision the detailed trimerization and resulting function of any given combination of the fiber knob proteins and their functional derivative/or analogue encompassed by these claims and whether they can produce the desired targeting effect.

Further, the specification fails to teach whether Ad5.fib16 would target all fibroblast-like and macrophage-like cells other than synovial cells. In fact, the prior art of record teaches that two strains of Ad11 isolated from two different patients differ in their binding ability to epithelial cells of various origins (*Mei et al*, Virol 1998;240:254-66). Thus, determination of the target effects of a particular fiber protein modification is not predictable until they are actually made and used, hence resulting in a trial and error situation. It is unpredictable without the undue experimentation to determine which fragment/or analog would function properly for a particular cell targeting effect.

Claims further embrace any nucleic acid vector, while it is known in the art that adenoviral vector has liver tropism, the specification is silent regarding the tissue tropism of other vectors, and whether incorporating an Ad5.Ad16 fiber protein would

alter tissue tropism for all known vectors, thus, fails to support the full scope of the invention. *Rudinger* (Peptide Hormones 1976; June;pages 1-7) teaches the relationship of sequence components and the peptide hormone function "THE SIGNIFICANCE OF PARTICULAR AMINO ACIDS AND SEQUENCES FOR DIFFERENT ASPECTS OF BIOLOGICAL ACTIVITY CANNOT BE PREDICTED *A PRIORI* BUT MUST BE DETERMINED FROM CASE TO CASE BY PAINSTAKING EXPERIMENTAL STUDY." (last paragraph of text on page 6).One cannot extrapolate the teachings of the specification to the scope of the claims because the skilled artisan cannot envision the detailed structures of vehicles encompassed by these claims, thus except the Ad5.Fib16.LacZ, one would not know how to use the invention without first carrying out undue experimentation to determine which of the vehicles, capsid proteins, chimeric fiber proteins would have the recited function. Therefore, in view of the limited guidance, the lack of predictability of the art, and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

Claims 1, 3-11, 18-22, 27, and 36-42, 45, and 46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for preferentially delivering an adenoviral vector comprising a chimeric Ad5 and AD16 fiber knob protein to synovial fibroblast cells *in vitro* or *in vivo* via intra-articular or peri-articular injection, does not reasonably provide enablement for delivering any vector, with any chimeric viral fiber protein, via any routes of administration, to any fibroblast-like or macrophage-like cells. The specification does not enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

Given the broadest reasonable interpretation, claim 27 is drawn to a method of delivering any nucleic acid vector having a tropism for fibroblast-like or macrophage-like cells in vivo via any route of administration. Although claim 27 does not require a particular therapeutic use, in light of the specification, the claims embrace an *in vivo* method for delivering foreign genes, thus, implicitly state the intended use of the method for a therapeutic use. With respect to claim breadth, the standard under 35 U.S.C. §112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. When analyzing the enabled scope of the claims, the intended use is to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. In light of the specification, "a

composition targeting specific cells in vivo and a method for delivering nucleic acid" is defined as a composition for therapeutic use, to prevent, alleviate, treat, or cure a disease within the animal to which the substance is administered, therefore, will be evaluated by the standard. As such, the broadest reasonable interpretation of the claimed invention properly encompasses gene therapy for fibroblast-like or macrophage-like cells; therefore, the claims will be evaluated by that standard.

In view of the specification, it teaches construction of recombinant adenoviral virus having modified fiber knob proteins, particularly the combination of ad5 and ad16, it teaches transfection and relative efficiency of said vector *in vitro*, and *in vivo* in a monkey model via intra-articular or peri-articular injection, and it demonstrates that recombinant adenoviral vector Ad5 carrying the fiber of Ad16 infects hyperplastic synovium more efficiently than that of the fiber of Ad5 and as compared to the chondrocytes (example 7). However, the specification fails to teach the genus of vectors having said tissue tropism, whether any type of vector carrying an adenoviral vector fiber 16 would achieve the desired effect, whether the effect extends to any type of fibroblast-like or macrophage-like cells, whether any route of administration, such as intramuscular, intradermal, intravenous, and oral administration would also achieve the preferential transfection effect, therefore, fails to provide an enabling disclosure to support the full scope of the claims.

In view of the state of the art, several vector systems are in use for somatic gene transfer. These include DNA (either naked or complexed), RNA viruses (retroviruses), and DNA viruses (adenovirus, adenoassociated virus, herpesvirus and poxvirus). Each

system has perceived different tissue tropism, advantages and disadvantages in gene delivery, which influence their selection for current or projected clinical applications. For example, adenoviral vector is efficient in cell entry and wide range of host cells, but highly immunogenic and remain episomal, difficult to obtain long-term stability, thus better suited for use in vaccination or transient gene expression; transfection of retroviral vector is limited to dividing cells; AAV requires replicating adenovirus (helper virus) to grow and has very limited insert size. herpes are highly immunogenic and the transgene is shut down within one week after infection for a variety of target cells, (*Robbins et al*, Pharmacol Ther 1998;80:35-47, entire article, sections 2.2, 2.3 particularly) therefore, they would not be suitable for long term delivery of a foreign gene. Herpes and pox viruses are also highly immunogenic. Naked DNA is extremely inefficient in entry, and no mechanism for persistence or stability. (Orkin et al, Dec. 1995, pages 21-23, 30-32). For *in vivo* gene therapy in a patient, these are the factors have to be considered. *Verma et al* (Nature 1997;389;239-42) teach "THE USE OF VIRUSES IS A POWERFUL TECHNIQUE, BECAUSE MANY OF THEM HAVE EVOLVED A SPECIFIC MACHINERY TO DELIVER DNA TO CELLS. HOWEVER, HUMANS HAVE AN IMMUNE SYSTEM TO FIGHT OFF THE VIRUS, AND OUR ATTEMPTS TO DELIVER GENES IN VIRAL VECTORS HAVE BEEN CONFRONTED BY THESE HOST RESPONSE" (last paragraph of left column on page 239). The specification fails to teach how to overcome the aforementioned difficulties in the art, and the specification fails to teach whether any vector, and any serotype adenovirus (other than Ad5) carrying a fiber of Ad16 would achieve desired vector targeting. It would have required undue experimentation for the skilled artisan intending to practice the instant invention.

Miller et al (1995, FASEB J., Vol. 9, pages 190-199), acknowledge various vector system available in the art, then teach, "NO SINGLE DELIVERY SYSTEM IS LIKELY TO BE UNIVERSALLY APPROPRIATE, FOR INSTANCE, THE REQUIREMENTS OF GENE THERAPY FOR CYSTIC FIBROSIS ARE GREATLY DIFFERENT FROM THOSE OF CANCER" (1st paragraph, page 190). "ONCE AGAIN, TARGETING AT THE LEVEL OF THE VECTOR HAS NOT YET BEEN PARTICULARLY WELL DEVELOPED; HENCE, LIPOSOME OR VIRAL-MEDIATED DELIVERY OF THE CFTR GENE TO AIRWAY EPITHELIAL CELLS OF CF PATIENTS HAS RELIED LARGELY ON THE LOCALIZED DELIVERY OF THE VECTORS DIRECTLY TO THE AFFECTED TISSUES" (1st paragraph, page 198) *Makrides et al* (Protein Exp Pur 1999;17:183-202) teach "THE CHOICE OF AN EXPRESSION SYSTEM FOR PRODUCTION OF RECOMBINANT PROTEINS DEPENDS ON MANY FACTORS, INCLUDING CELL GROWTH CHARACTERISTICS, EXPRESSION LEVELS, INTRACELLULAR AND EXTRACELLULAR EXPRESSION, POSTTRANSLATIONAL MODIFICATIONS AND BIOLOGICAL ACTIVITY OF THE PROTEIN OF INTEREST, AS WELL AS REGULATORY ISSUES AND ECONOMIC CONSIDERATIONS IN THE PRODUCTION OF THERAPEUTIC PROTEINS."

The routes of administration are one of the critical factors for achieving desired selective gene delivery. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired cells *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, *Deonarain* (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ABILITY TO TARGET A GENE TO A SIGNIFICANT POPULATION OF CELLS AND EXPRESS IT AT ADEQUATE LEVELS FOR A LONG ENOUGH PERIOD OF TIME" (page 53, first paragraph). Deonarain reference gives high hope to targeted gene delivery, but the discussed strategies are still under investigation, and at

the time, they were much less efficient than viral gene delivery (Conclusion), "GENE DELIVERY BY LIGAND TARGETED RECEPTOR-MEDIATED ENDOCYTOSIS OF POLYPLEXES *SHOULD* FIND ITS WAY INTO SOME MAIN LINE GENE THERAPY TREATMENT SCHEMES... HOWEVER, IN ORDER TO ACHIEVE THE LEVELS OF GENE TRANSFECTION AND EXPRESSION SEEN WITH RETROVIRAL VECTORS, FURTHER ADVANCES NEED TO BE MADE IN FIELDS SUCH AS MAMMALIAN ARTIFICIAL CHROMOSOMES" (paragraph bridging pages 65-66). Therefore, while the specification teaches that i.v. administration of Ad5.Luc-fib16 leads to a reduced liver cell transfection compared to Ad5.Clip.Luc, the vector still predominantly distributed in the liver and spleen, and also at a noticeable level in lung, kidney, heart and brain (table II). The specification fails to teach whether the vectors would reach synovial cells or any other fibroblast-like or macrophage-like cells via intravenous injection. Thus, it fails to provide a sufficient disclosure to support the full scope of the claims.

The claims further read on a therapeutic method in vivo, however, the specification fails to provide any therapeutic effect as a result of recombinant adv transfection even though the experiments were performed in an experimental arthritis model. Applicants are reminded that the preferential transfection of hyperplastic cells does not necessarily support a therapeutic effect as taught by the following skilled artisans. The nature of the claims being gene therapy, the state of the art is still under development and highly unpredictable. *Russell et al* (Nat Genet 1998 Apr; 18:325-30) review "IT IS CURRENTLY POSSIBLE TO INTRODUCE DEFINED MUTATIONS INTO MAMMALIAN CHROMOSOMES BY GENE TARGETING USING TRANSFECTION (ELECTROPORATION OR CALCIUM-PHOSPHATE PRECIPITATION) OR MICROINJECTION METHODS. TRANSFECTION TECHNIQUES USUALLY PRODUCE HOMOLOGOUS RECOMBINATION EVENTS IN ONLY A SMALL FRACTION OF THE TOTAL CELL

POPULATION.(...) CHROMOSOMAL GENE-TARGETING EXPERIMENTS HAVE BEEN PERFORMED WITH RETROVIRAL AND ADENOVIRAL VECTORS, BUT THE RECOMBINATION RATES WERE NOT SIGNIFICANTLY HIGHER THAN THOSE OBTAINED BY TRANSFECTION. (2nd paragraph, page 325). *Boucher et al* (J Clin Invest 1999 Feb; 103:441-5) review that host cell resistance to foreign gene is another difficulty for successful in vivo gene transfer. "DESPITE AN IMPRESSIVE AMOUNT OF RESEARCH IN THIS AREA, THERE IS LITTLE EVIDENCE TO SUGGEST THAT AN EFFECTIVE GENE-TRANSFER APPROACH FOR THE TREATMENT OF CF LUNG DISEASE IS IMMINENT. THE INABILITY TO PRODUCE SUCH A THERAPY REFLECTS IN PART THE LEARNING CURVE WITH RESPECT TO VECTOR TECHNOLOGY AND THE FAILURE TO APPRECIATE THE CAPACITY OF THE AIRWAY EPITHELIAL CELLS TO DEFEND THEMSELVES AGAINST THE PENETRATION BY MOIETIES, INCLUDING GENE-THERAPY VECTORS, FROM THE OUTSIDE WORLD." *Zink et al* (Gene Ther Mol Biol 2001 Jan;6:1-24) teach the reasons why the transgene would fail to achieve the expected effect in vivo, and indicated that in addition to the interaction of transcription factors with specific DNA elements, the transcription of mammalian genes and transgenes integrated into mammalian genomes is regulated at the levels of chromatin structure and nuclear architecture, "TRANSCRIPTIONAL REGULATION OF INTEGRATING GENE THERAPY VECTORS IS ONLY WELL INVESTIGATED AT THE MOLECULAR LEVEL, FEW DATA EXIST REGARDING THE INVOLVEMENT OF CHROMATIN STRUCTURE, AND VIRTUALLY NOTHING IS KNOWN ABOUT THE INVOLVEMENT OF NUCLEAR CHROMOSOME- AND GENOME ARCHITECTURE. THEREFORE, IT IS NOT SURPRISING THAT THE EXPRESSIONAL BEHAVIOR OF GENE THERAPY VECTORS AFTER INTEGRATION IS OFTEN UNPREDICTABLE AND DIFFICULT TO IMPROVE" (abstract).

Thus, it is evident that at the time of the invention, the gene therapy practitioner, while acknowledging the significant potential of gene therapy, still recognized that such

therapy was neither routine nor accepted, and awaited significant development and guidance for its practice. Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for such therapeutic regimen. Although the instant specification provides a brief review of a potential therapeutic use of the claimed vector and data from ex vivo studies, it is not enabled for its full scope because the specification does not disclose whether the genus of nucleic acids delivery vehicles encompassed by the claims would targeting desired cells in vivo by any route of administration, any significant gene transfer in fibroblast-like and macrophage-like cells besides synoviocytes *in vivo* by any route of administration, or any therapeutic effects *in vivo*.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters for achieving *in vivo* gene expression in any and all fibroblast-like and macrophage-like cells *in vivo* at therapeutic levels, in particular for the treatment of any and all diseases, the lack of direction or guidance provided by the specification as well as the absence of working examples with regard to *in vivo* gene therapy of any and all diseases or disorders by all routes of administration, and the breadth of the claims directed to the use of numerous therapeutic genes/vectors/targeting elements combinations, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4, 18, 27, 35, 36, and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by *Maxwell et al* (US 5,585,254).

Claims are drawn to a nucleic acid delivery vehicle having at least a tissue tropism for fibroblast-like cells, but lacking or having reduced tropism for liver cells, wherein the tissue tropism may be provided by a virus capsid protein or a functional derivative thereof. The specification teaches that adenoviral serotype 2 or 5 are considered as efficient for transferring genes *in vivo* to the liver (Specification, page 8, lines 10-12), logically, vectors other than serotype 2 or 5 or modified Ad2 or Ad5 capsid proteins would be considered as having reduced liver tropism. Claim 27 is drawn to a method of delivering such vector to desired cells in vitro and in vivo.

Maxwell et al teach making a vector carrying a gene of interest that selectively targets a cell population, they teach that parvovirus-based vectors can be pseudotyped such that the vector is derived from a different viral capsid (pseudotype recombinant vectors), "THE ABILITY TO PSEUDOTYPE RECOMBINANT VECTORS OF THE PRESENT INVENTION GREATLY EXTENDS THE HOST RANGE OF THE VECTORS AND PERMITS ADDITIONAL TARGETING

STRATEGIES FOR GENE TRANSFER" (column 14, lines 44-54). For targeting fibroblasts, encapsulating the vector in an MVMp capsid (column 14, line 63). In working example 10, they made a pseudotyped recombinant LuIII vector in an MVMp capsid. Since the pseudotype recombinant vectors taught by *Maxwell et al* target fibroblasts not liver cells, they meet the claim limitation. *Maxwell et al* teach a method of using such vector for in vitro transfection (claims 70 and 71). Therefore, *Maxwell et al* anticipate the instant claims.

Claims 1-8, 10, 11, 18-21, 27, 35-38, 41, 43, and 44 are rejected under 35 U.S.C. 102(b) as being anticipated by *Stevenson et al* (J Virol 1997;6:4782-90).

Claims are drawn to a nucleic acid delivery vehicle having at least a tissue tropism for macrophage-like or fibroblast-like cells, but lacking or having reduced tropism for liver cells, wherein the tissue tropism is provided by a virus capsid or a functional derivative thereof, wherein the tissue tropism may be provided by a chimeric fiber protein from Adv subgroups B and C, or B and not B, or subgroups B and B (e.g. see claims 7, 8, 10, & 11; or 7 & 39, respectively), any vector having such features would be considered to meet the claim limitation for tissue tropism for fibroblast-like or macrophage-like cells.

Stevenson et al teach a chimeric fiber cDNA containing the Ad3 (subgroup B) fiber head domain fused to the Ad5 (subgroup C) fiber tail and shaft (capsid fiber protein) incorporated into the genome of an adenovirus vector with E1 and E3 deleted, and encoding β-galactosidase (nucleic acid of interest, see abstract). The vector has a

modified Ad5 capsid protein and a capsid comprising proteins from subgroups B and C, thus, meet claim limitation. *Stevenson et al* go on to teach transfecting fibroblast cells (MRC-5) *in vitro* using such vectors (figs. 4-6). Therefore, *Stevenson et al* anticipate the instant claims.

Please note that the claim recitation "having at least a tissue tropism for fibroblast-like or macrophage-like cells" or "having at least partially reduced tissue tropism for liver cells" have not been given patentable weight in the instant rejection because the preamble does little toward defining structure of the claimed vector. Rather, the structure or polynucleotide sequences are relied upon for determination.

Claims 1-6, 18, 35, 36, 43 are rejected under 35 U.S.C. 102(e) as being anticipated by *Wickham et al* (US 6,329,190), and as evidenced by *Lazarovits et al* (J Immunol 1994;151:6482-9).

Wickham et al teach a vector comprising a chimeric adv fiber protein that is more efficient than entry into cells of a wild-type adv fiber protein (abstract), wherein the chimeric fiber protein is hybrid between an Ad5 fiber shaft and a Ad2 fiber knob (both of subgroup C, fig. 1). They particularly teach a plasmid vector contains YIGSR targeting motif that binds to the high affinity laminin receptor, which could be useful in targeting the vector to fibroblast cells (paragraph bridging columns 28 & 29). They also teach ligands for the α4 integrins could target the vector to fibronectin, and VCAM-1 (column 28, lines 37-39), which would be useful for targeting synovial cells because *Lazarovits et al* teach these receptors are natural ligands for α4 integrins, and are present in the synovial fibroblasts and endothelial cells as a mechanism for inflammatory cell migration. Therefore, *Wickham et al* anticipate the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Wickham et al* (US 6,329,190).

Wickham et al teach targeting adenoviral vectors carrying a gene of interest to various desired cells via capsid protein and other antibodies, and ligands (column 3, lines 9-42). They specifically teach a plasmid vector contains YIGSR targeting motif that binds to the high affinity laminin receptor, which could be useful in targeting the vector to fibroblast cells (paragraph bridging columns 28 & 29). They also teach a LVD targeting sequence could target the vector to macrophages (column 28, lines 30-33),

and ligands for the α4 integrins could target the vector to fibronectin, and VCAM-1 (column 28, lines 37-39), which are present in synoviocytes. *Wickham et al* do not particularly transfecting a synovial cell with the targeting vector. However, the working examples illustrated that cell transfection is routine in the art.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the targeting molecules taught by *Wickham et al* in making a nucleic acid delivery vehicle comprising the gene of interest with a tissue-tropism to synovial cells with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to make such a vector for specific cell targeting to enhance the desired gene delivery effects. Thus, the claimed invention as a whole was clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-4, 18, 27, 35, 36, and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Goldsmith et al* (US 5,861,290).

Goldsmith et al teach how to make a vector that selectively targets macrophages, "ISOLATED HIV-1SF162 IS NATURALLY SELECTIVE FOR MACROPHAGE INFECTION, THUS, BY PACKAGING THE VECTOR IN AN HIV-1SF162-DERIVED ENVELOPE, TARGETING TO THE MACROPHAGES CAN BE EFFECTED" (column 15, lines 31-36), and the detailed method steps of making such (column 21, lines 36-43).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the method taught by *Goldsmith et al* making a nucleic acid delivery vehicle comprising the gene of interest with a tissue-tropism to

macrophages but not liver cells, and using such for transfecting said cells in vitro or locally with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to make such a vector for specific cell targeting to enhance the desired gene delivery effects. Thus, the claimed invention as a whole was clearly *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed. Claims 9, 22, 40, 45, and 46 appear to be free of the cited prior art of record, however, they are subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
December 9, 2002

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER